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Unchanged Incidence of Severe Retinopathy in a Population of Type 1 Diabetic Patients with Marked Reduction of Nephropathy

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The incidence of nephropathy in Type 1 diabetes mellitus has declined during the past decade, probably as a result of improved glycaemic control. We wanted to investigate whether the incidence of severe retinopathy has changed during the same time period and to evaluate the importance of glycaemic control in relation to the development of severe retinopathy and nephropathy. All 213 patients in whom Type 1 diabetes mellitus was diagnosed before the age of 15 years between 1961 and 1980 in a district in south-eastern Sweden were studied. Ninety-two per cent of the patients were followed from the onset of diabetes to 1991 or to death. The cumulative incidence of severe retinopathy was not significantly different between the patients with diabetes onset 1961–65, 1966–70, 1971–75, and 1976–80. The risk of developing severe retinopathy or nephropathy was higher in patients with very poor glycaemic control ($HbA_{1c} \geq 8.4$ %) vs patients with poor control ($HbA_{1c} \geq 7.2 < 8.4$ %; $p < 0.001$). Patients with poor control had an increased risk of developing severe retinopathy vs patients with good control ($HbA_{1c} < 7.2$ %; $p < 0.008$) but there was no difference in the risk of nephropathy. No patients with good control developed nephropathy and only one patient developed severe retinopathy during 25 years of diabetes. © 1998 John Wiley & Sons, Ltd.

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Introduction

Improved glycaemic control has been shown to decrease the incidence of nephropathy and to slow the progression of retinopathy among patients with Type 1 diabetes mellitus (Type 1 DM).[1–3] For those delivering diabetes care, a key issue is to what extent the findings of the DCCT and other studies can apply to the wider population of Type 1 DM patients.[1–3] Only a few epidemiological studies have examined the prevalence of both retinopathy and nephropathy[4–6] and little is known about their simultaneous cumulative incidence.[7] One would hope to find decreased incidence of both these complications as there have been substantial changes in the treatment of diabetes in the past 25 years. The probability of a glycaemic threshold for retinopathy[6,8] and microalbuminuria[9] has aroused much interest. The question remains, however, whether there is a specific haemoglobin range at which the benefits of diabetes management is maximal.[10]

We began a prospective, population-based, long-term follow-up study of complications in young patients less than 15 years old with Type 1 DM starting in 1973, at the University Hospital, Linköping, Sweden. We studied all patients diagnosed during two decades (1961 to 1980) in the catchment area. We reported earlier that during the last decade the cumulative incidence of diabetic nephropathy up to 25 years' DM duration has decreased from 30 % to less than 10 %, probably as a result of improved glycaemic control.[11] We report here on the incidence of severe retinopathy and nephropathy in the same population and the importance of glycaemic control in the relation to the development of severe retinopathy and nephropathy.

Patients and Methods

We studied all 213 patients with Type 1 diabetes mellitus with onset before the age of 15 years, who lived within the catchment area of the Paediatric Clinic, University

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Hospital, Linköping, Sweden, between 1961 and 1980. One hundred and ninety-seven of the patients (92.5 %) were followed from the onset of diabetes to 1991 or to time of death (10 patients). The remaining 16 patients (8 %) were followed to their most recent clinic visit.

Patients were divided into four groups, according to year of diagnosis of diabetes, for the analysis of cumulative incidence of retinopathy: 1961–1965, 1966–1970, 1971–1975, and 1976–1980. The groups were similar in numbers of patients, sex distribution, mean age of onset of diabetes and follow-up (Table 1). During the 1960s, the standard insulin regimen was a single morning dose of long-acting insulin, sometimes with an additional dose of short-acting insulin. Patients were advised to eat regular meals and to limit intake of simple carbohydrates and fat. In 1971, a team consisting of doctors, a diabetes teaching nurse, a dietician, a social worker and, a few years later, a psychologist, was introduced to the clinic. Patients were seen at least every 3 months until they left school at the age of 18 to 20 years, at which time their care was transferred to the Department of Internal Medicine, where the same routines were followed. The number of daily insulin injections increased from 1 to 2 in the early 1970s, to 2 to 3 at the end of 1970s and from 3 to 4 or even 5 in the 1980s, a change that was facilitated by the introduction of pen injectors in 1984. With the introduction of more injections per day, the proportion of short-acting insulin increased from 10 to 20 % in the early 1970s to 60 % in the 1980s, when some patients used insulin pumps. Regular self-monitoring of urine glucose three times daily became routine in 1971 and self-monitoring of blood glucose and regular measuremnt of glycosylated haemoglobin began in 1980. Psychosocial support, group education, camps and regular evening lectures for parents also became important elements in the treatment programme in the early 1970s.[12]

After 5 years' duration of diabetes, patients were regularly screened for occurrence of retinopathy by ophthalmoscopy up to the 1970s and from the 1980s by using fundus photography evaluated by ophthalmologists. The onset of severe retinopathy was defined as the date of the first laser treatment. The indication for the treatment was proliferative retinopathy in all cases (confirmed by ophthalmologist review).

All patients were tested for proteinuria at their regular clinic visits using Albustix (Ames, Bridgend, England). The 154 patients (76 %) who still lived in our catchment area were invited to a special follow-up visit during 1990–92, and asked to collect three timed overnight urine samples for measurement of the albumin excretion rate to confirm the diagnosis of proteinuria. One hundred and twenty-two (79 %) completed the tests. The remaining 32 patients were examined at routine clinic visits. Thirty of the 49 patients who had moved out of the area responded to a questionnaire and provided data (via their physicians) on albumin excretion rates, antihypertensive treatment, data on laser treatment if any and glycated haemoglobin values.

Diabetic nephropathy was defined as persistent albuminuria (1+ Albustic > 300 mg l^{-1}). The first year in which albuminuria was persistent was defined as the year of onset of diabetic nephropathy.

Glycated haemoglobin was determined with ion exchange chromatography. Between 1980 and November 1984 mini-columns were used (Quicksep, Isolab, Akron, USA) and the analysis included the labile Schiff-base fraction. Elimination of the labile Schiff-base fraction was made from 15 April 1982. A HPLC method determining HbA_1 was applied from 15 November 1984 (HPLC: Auto A1c HA 8810, Kyoto Daichi, Kyoto, Japan). The results were first given as HbA_1, and since 25 April 1986 as HbA_{1c}. From the HbA_1 measurements corresponding HbA_{1c} values were calculated according to inter-method calibrations made by the analysing laboratory. Our reference range for the HbA_{1c} method was 3.2–6.0 % HbA_{1c} (95 % confidence interval for the mean of HbA_{1c} measurements on non-diabetic subjects). Normal range for the mini-column method used corresponds well with this interval when transformed. Every HbA_{1c} value from each patient was included in the analysis. To evaluate if the glycaemic control has the same impact on the development of both severe retinopathy and nephropathy, the patients were grouped

Table 1. Clinical characteristics of patients with Type 1 diabetes mellitus

Year of onset of diabetes	*N*	Per cent men	Mean age at onset (yr)	Per cent of patient follow-up	Patients with severe retinopathy after 20 yr (*n*)	Cumulative incidence of severe retinopathy after 20 yr (% ± SE)	Patients with diabetic nephropathy after 20 yr (*n*)	Cumulative incidence of diabetic nephropathy after 20 yr (% ± SE)	Mean HbA_{1c} 1980–1985 % (SE)	Mean HbA_{1c} 1986–1991 % (SE)
1961–1965	57	42.1	8.4	87.7	13	26.5 ± 6.3	13	28.0 ± 6.3	7.6 ± 0.2	7.1 ± 0.2[b]
1966–1970	50	48.0	8.0	88.0	6	13.5 ± 5.1	4	8.9 ± 4.3	7.3 ± 0.2	6.7 ± 0.2[b]
1971–1975	55	52.7	8.7	96.4	8	15.9 ± 5.2	3	5.8 ± 3.2	7.6 ± 0.2	7.1 ± 0.2[b]
1076–1980	51	39.2	8.7	98.0	–[a]	–[a]	–[a]	–[a]	7.0 ± 0.2	7.0 ± 0.2
Total	213	45.5	8.5	92.5	27	–	21	–	7.4 ± 0.1	7.0 ± 0.1[b]

[a]Values are not shown because of insufficient length of follow-up.
[b]Significant improvement between the time periods $p < 0.01$.

Table 2. Degree of glycaemic control before complication or to end of study

Group according to glycaemic control	Times upper normal HbA_{1c} value (%)	Corresponding Linköping HbA_{1c} value (%)	Calculated corresponding DCCT HbA_{1c} value (%)
Good	< 1.2	< 7.2	< 8.2
Poor	$1.2 \leq 1.4$	$7.2 \leq 8.4$	$8.2 \leq 9.4$
Very poor	1.4	> 8.4	> 9.4

according to degree of glycaemic control (mean value of HbA_{1c}) before the complication or to the end of study, into good (< 1.2 non-diabetic HbA_{1c} value [$n = 81$]), poor ($\geq 1.2 < 1.4$ [$n = 66$]) and very poor (≥ 1.4 [$n = 33$]; Table 2). All patients with data on glycaemic control before the onset of complication were included in the analyses of the role of different glycaemic control for the development of severe retinopathy and nephropathy (Table 3). Glycaemic control was followed until the clinical diagnosis of a complication.

The measurements of HbA_{1c} from our laboratory in Linköping and that used in the DCCT have been directly compared but discussion and comparison about the exact values from other laboratories are difficult to evaluate due to different methodology and lack of standardization[13] (Table 2). The study was approved by the Ethical committee of the Medical Faculty, University of Linköping and all patients gave informed consent for the 1990–1992 study.

Statistical Analyses

The cumulative incidence of complications was calculated for 1-year intervals using a life-table method which takes into account varying intervals of follow-up after the first visit. Patients who had not developed nephropathy or severe retinopathy contributed person-years of follow-up until examination, in 1990–1992 if they were studied then, the year of their last clinic visit, or the year of death. The calculations were performed according to the algorithm of Lee and Desu (1972), using the SPSS Statistical Package for the Social Sciences.[14]

Results

The Cumulative Incidence of Severe Retinopathy

The cumulative incidence of severe retinopathy in the cohort with diabetes onset 1961–65 started to increase after a diabetes duration of 10 years and continued to rise up to a duration of 30 years when it reached 54.5 % (Figure 1(a)). In the cohort with diabetes onset 1966–70, severe retinopathy started to increase in incidence after 10 years and reached 43.4 % after 25 years. The cumulative incidence of severe retinopathy in the cohort with onset 1971–75 followed the first cohort and 16 % of the patients had developed severe retinopathy by 20 years' duration of diabetes. None of those with onset 1976–80 developed severe retinopathy during the study period. There was no significant decline in the cumulative incidence of severe retinopathy between any of the cohorts. The cumulative incidence of nephropathy in the same cohorts was markedly reduced in the later ones as previously published and this is shown for comparison[4] (Figure 1(b)).

Incidence Rate of Severe Retinopathy

The incidence rate of severe retinopathy increased with time after a diabetes duration of 8 years and continued to increase to 6/100 person-years after a diabetes duration of over 25 years. In contrast the risk of developing diabetic nephropathy reached a peak within 20 years after the onset of diabetes and declined thereafter (Figure 2). The combination of severe retinopathy and diabetic nephropathy was more common than severe retinopathy alone in patients with onset 1961–1965 ($p = 0.008$), while severe retinopathy alone was more common in patients with onset 1966–1980 ($p = 0.001$) (Figure 3).

Table 3. Role of glycaemic control in the development of severe retinopathy and nephropathy

Group according to glycaemic control	Retinopathy			Diabetic nephropathy		
	Number of patients at start	Patients with severe retinopathy after 20 yr (*n*)	Cumulative incidence of severe retinopathy after 20 yr (% ± SE)	Number of patients at start	Patients with diabetic nephropathy after 20 yr (*n*)	Cumulative incidence of diabetic nephropathy after 20 yr (% ± SE)
Good	81	1	1.9 ± 1.8	84	0	0
Poor	66	4	9.0 ± 4.4	69	2	4.3 ± 3.1
Very poor	33	13	55.5 ± 10.7	28	7	36.3 ± 11.7
Total	180	27	–	181	9	–

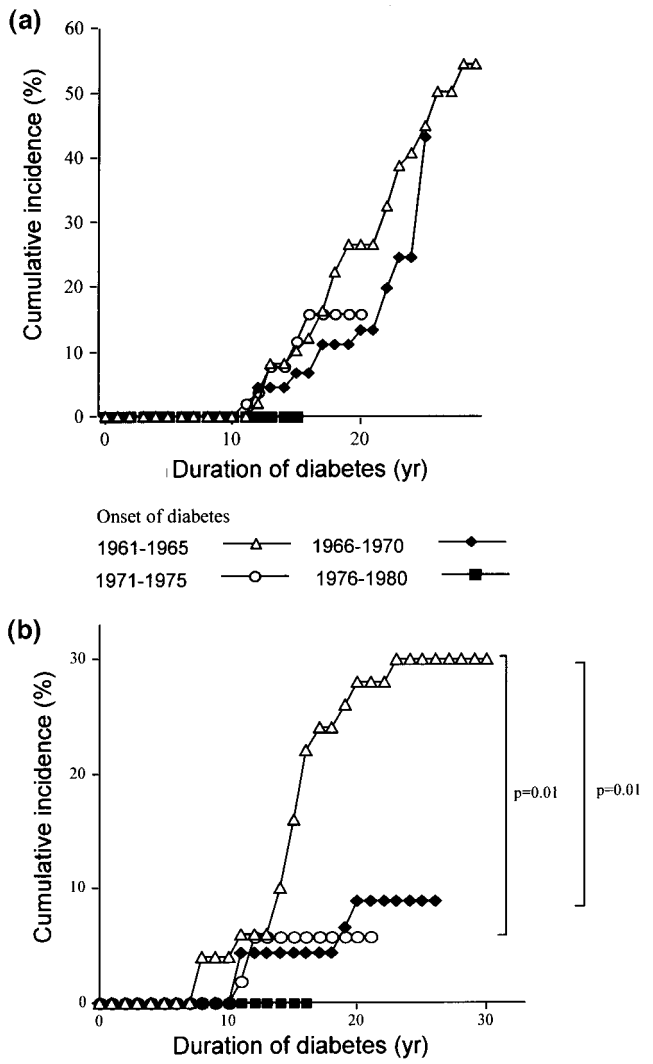

Figure 1. (a) Cumulative incidence of severe (laser treated) retinopathy among patients in whom insulin-dependent diabetes began before the age of 15 years, according to year of onset. (b) Cumulative incidence of persistent albuminuria among patients in whom insulin-dependent diabetes began before the age of 15 years, according to year of onset. (Reprinted by permission of *N Engl J Med* 1994; **330**: 15–18)

The Importance of Glycaemic Control

The cumulative incidence of severe retinopathy was similar in the three different groups of glycaemic control until approximately 10 years' duration of diabetes. From 15 years onward, the cumulative incidence of severe retinopathy in those with very poor control (HbA_{1c} > 8.4 %) increased to 85 % after 25 years of diabetes. The incidence of severe retinopathy in those with poor control (HbA_{1c} 7.2-< 8.4 %) began to increase after 12 years and reached 40 % after 25 years ($p < 0.001$ in comparison to very poor control). Only 1 patient with good control developed severe retinopathy during 25 years ($p < 0.008$ in comparison to poor control) (Figure 4(a)). In patients with very poor control the cumulative incidence of nephropathy began to increase after 11 years, reached 36 % after 20 years and remained constant

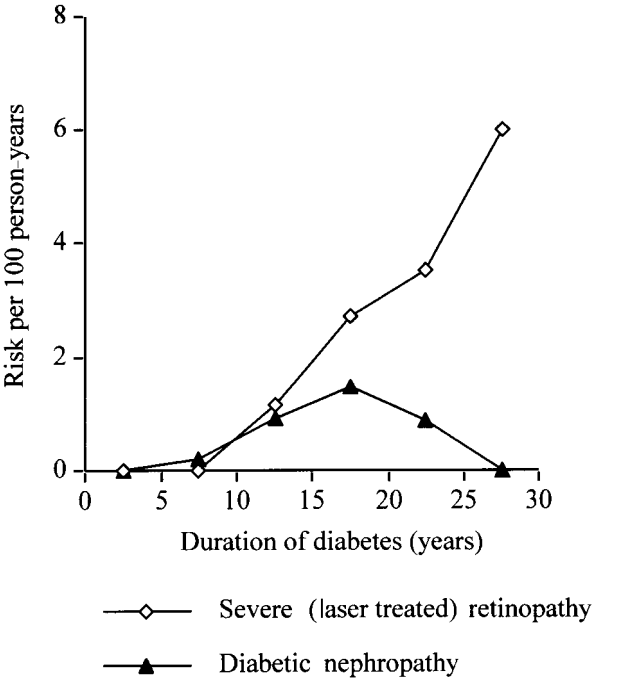

Figure 2. Incidence rate (incident case/100 person-years; *y*-axis) of severe retinopathy (squares) and nephropathy (triangles) in relation to diabetes duration (years; *x*-axis)

thereafter to the end of the observation period. Four per cent of the patients with poor control developed nephropathy ($p < 0.001$) but none with good control during 25 years' duration of diabetes (Figure 4(b)).

Discussion

We found no significant decrease in the cumulative incidence of severe retinopathy between the different cohorts of patients diagnosed with diabetes between 1961–65, 1966–70, 1971–75 or 1976–80. This is in marked contrast to the cumulative incidence of nephropathy in the same population, which simultaneously decreased from 30 % to less than 10 %.[11] The simultaneous presence of both severe retinopathy and nephropathy in many patients had led investigators to assume that they either have a common pathogenesis or that diabetic nephropathy is a risk factor for proliferative retinopathy[15] or vice versa.[16] Our data show that a decline in incidence of nephropathy was not followed by the same decline in incidence of severe retinopathy (Figure 3).

A similar dissociation between the changes in the cumulative incidence of diabetic nephropathy and severe retinopathy has earlier been observed as the Joslin clinic with a decrease in nephropathy but an unchanged incidence of retinopathy.[17] They also found that the incidence rate of retinopathy increased with diabetes duration while the incidence rate of nephropathy had a bell-shaped curve, as in our study.[17]

We included only patients who lived in our catchment area (260 000 inhabitants) at the time of diagnosis. In

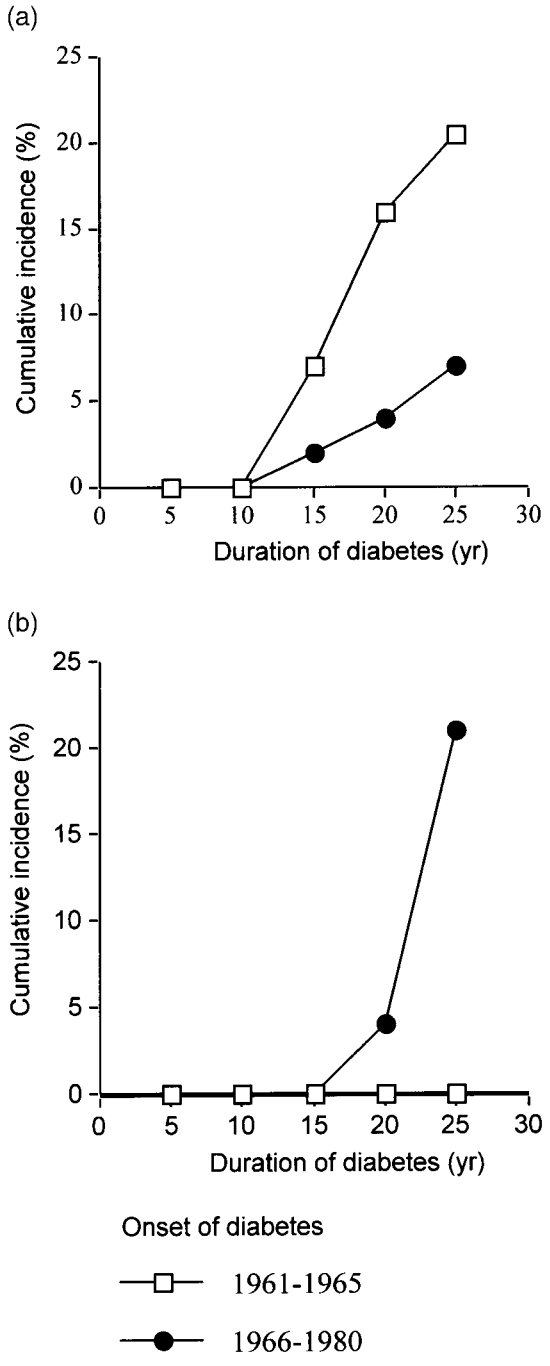

Figure 3. (a) Cumulative incidence of patients with the combination of severe retinopathy and nephropathy according to year of diabetes onset. (b) Cumulative incidence of patients with severe retinopathy without nephropathy according to year of diabetes onset

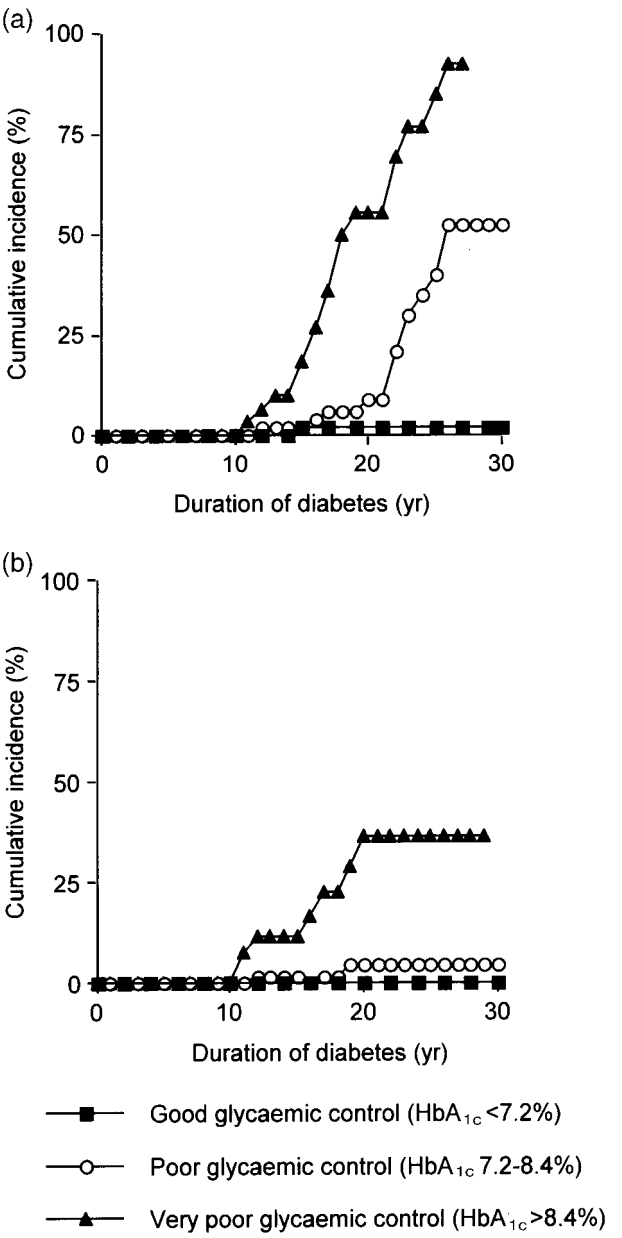

Figure 4. Cumulative incidence of (a) severe retinopathy and (b) diabetic nephropathy with increasing diabetes duration in relation to glycaemic control. The patients were grouped according to degree of glycaemic control (mean value of HbA_{1c}) before the complication

Sweden, all children with diabetes are treated at a hospital paediatric clinic, so we can be confident that our study population is not biased. The population represents all social classes but was ethnically homogeneous at the time of recruitment. With a high follow-up rate, our ascertainment of incidence of complications is likely accurately to reflect the incidence among all patients with Type 1 DM.

The date of laser treatment was used to define the onset of severe retinopathy, since this is more exact than the date of diagnosis, and the reason for laser treatment was confirmed as proliferative retinopathy on review. Methods for screening for retinopathy changed during the follow-up period, from opthalmoscopy to fundal photography and we cannot be sure that proliferative retinopathy was diagnosed as early before the introduction of photography. This may hide a small difference in the cumulative incidence of severe retinopathy between the different cohorts.

We believe the reduction in nephropathy seen in more recently-diagnosed diabetes relates to improved glycaemic control. The definition of diabetic nephropathy

(persistent proteinuria) was similar to that used in other studies.[18,19] Only four patients—two in the group in which diabetes developed between 1961 and 1965—received antihypertensive treatment before the onset of nephropathy,[11] so the observed reduction of nephropathy was not related to the use of this treatment. A recent report by Rossing *et al.* failed to find a declining incidence of nephropathy in a population from Copenhagen, probably a result of unchanged glycaemic control.[20] All patients in the Stockholm study who developed nephropathy within 3 years had HbA_{1c} levels above 9 % (non-diabetic range 4–6 %).[17] A recent cross-sectional study suggests that the risk of microalbuminuria increases abruptly above HbA_{1c} levels of 8.1 % (calculated DCCT value).[21] The degree of glycaemic control seems to influence the progress from microalbuminuria to overt nephropathy, since microalbuminuria in our patients did not progress to persistent proteinuria if the mean glycaemic control was less than 8 %.[22] One-third of the patients with very poor control developed nephropathy during 20 years of diabetes, as during the 1940s.[18] The patients in our study with good control or poor control had a low risk of nephropathy. However, it is likely that poor glycaemic control needs to be combined with genetic factors[10] as 64 % of our patients with very poor control did not develop nephropathy.

There is also evidence linking glycaemic control with risk of retinopathy. The DCCT reports a continuous increase of the risk of retinopathy with higher HbA_{1c} levels in patients using intensive treatment regimes.[1] However the risk of progress in retinopathy increased two to three fold between deciles of HbA_{1c} 8 and > 9 %.[8] It had earlier been reported that all patients developing retinopathy and requiring laser treatment had HbA_{1c} levels greater than 8.5 %.[23] In the Berlin Retinopathy Study, a non-linear discontinuous relationship was found between long-term glycaemic control and early background retinopathy, with a threshold level of $HbA_{1c} > 9$ % (non-diabetic range up to 6 %). The incidence of background retinopathy in those with mean HbA_{1c} below 7 % was very low.[8] In the Eurodiab IDDM complications study, the incidence of proliferative retinopathy began to rise at a HbA_{1c} level above 8 % (non diabetic range 2.9–4.8 %)[6] and the risk of developing severe retinopathy was very low among those patients with good control in our study. The group of patients with poor control postponed their onset of severe retinopathy but 40 % still developed the complication during 25 years of diabetes. Near all of the patients with very poor control had developed severe retinopathy by 25 years of diabetes.

The Stockholm Study showed a difference in cumulative incidence of persistent albuminuria between the intensified treatment group and the standard treatment group after 60 months[21] but took more than 90 months before a difference in cumulative incidence of serious retinopathy occurred.[2] Our population reached a mean of HbA_{1c} level below 7.2 % only during the last 6 years, which may not be long enough. The group with diabetes onset 1976–1980 had a mean value of HbA_{1c} 7.1 % during the whole time period and nobody in this group developed severe retinopathy or nephropathy during the study period.

Our study is too small to find out if there are any threshold effects of glycaemic control and no study so far have been able to follow glycated haemoglobin from onset of diabetes until a diabetes duration of 20–25 years. The comparison with other studies is hampered by the lack of international standardization of HbA_{1c} measurements. However, our study suggests that the risk of severe retinopathy increases considerably at a glycated haemoglobin value about 7.2 % while the same increase of risk of nephropathy starts at about 8.4 %. This may explain why improvements in the treatment of diabetes during the last 20 years has been followed by a decrease in cumulative incidence of nephropathy[4] but not a decrease of severe retinopathy, so far, in our population of Type 1 DM patients.

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References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–986.
2. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993; **329**: 304–309.
3. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of Type 1 diabetes. *Lancet* 1993; **341**: 1306–1309.
4. Parving H-H, Hommel E, Mathiesen E, Skott P, Edsberg B, Bahnsen M, *et al.* Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. *Br Med J* 1988; **296**: 156–160.
5. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, *et al.* Prevalence of complications in IDDM by sex and duration: Pittsburg epidemiology of diabetes complications study 11. *Diabetes* 1990; **39**: 1116–1124.
6. Stephenson J, Fuller JH, the Eurodiab IDDM Complications Study Group. Microvascular and acute complications in IDDM patients: the Eurodiab IDDM complications study. *Diabetologia* 1994; **37**: 278–285.
7. Krolewski AS, Warram JH, Rand LI, Kahn RC. Epidemiologic approach to the etiology of Type 1 diabetes mellitus and its complications. *N Engl J Med* 1987; **317**: 1390–1398.

8. Danne T, Weber B, Hartmann R, Enders I, Burger W, Hovener G. Long-term glycemic control has a non-linear association to the frequency of background retinopathy in adolescents with diabetes. *Diabetes Care* 1994; **17**: 1390–1396.
9. Krolewski AS, Laffel LM, Krolewski M, Quinn M, Warram JH. Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1995; **332**: 1251–1255.
10. Dahl-Jörgensen K, Brinchmann-Hansen O, Bangstad H-J, Hanssen KF. Blood glucose control and microvascular complications—what do we do now? *Diabetologia* 1994; **37**: 1172–1177.
11. Bojestig M, Arnqvist AJ, Hermansson G, Karlberg BE, Ludvigsson J. Declining incidence of nephropathy in insulin-dependent diabetes mellitus. *N Engl J Med* 1994; **330**: 15–18.
12. Ludvigsson J. Metabolic control in juvenile diabetes mellitus. The influence of some biochemical and socio-psychological factors. University of Linköping Medical Dissertations. No. 42, 1976.
13. Kullberg CE, Bergström A, Dinesen B, Larsson L, Little RR, Goldstein DE, Arnqvist HJ. Comparisons of studies on diabetic complications hampered by differences in GHb measurements. *Diabetes Care* 1996; **19**: 726–734.
14. SPSS Inc. *Statistical Package for the Social Sciences: SPSS for the Macintosh*. SPSS Inc., 1990.
15. Klein R, Klein BEK, Moss SE. Epidemiology of proliferative diabetic retinopathy. *Diabetes Care* 1992; **15**: 1875–1891.
16. Stephenson JM, Fuller JH, Viberti GC, Sjolie AK, Navalesi R, the Eurodiab IDDM Complications Study Group. Blood pressure, retinopathy and urinary albumin excretion in IDDM: the Eurodiab IDDM complications study. *Diabetologia* 1995; **38**: 599–603.
17. Krolewski AS, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR. Risk of proliferative diabetic retinopathy in juvenile onset type 1 diabetes: a 40-yr follow up study. *Diabetes Care* 1986; **9**: 443–452.
18. Krolewski AS, Warram JH, Christlieb AR, Busick EJ, Kahn CR. The changing natural history of nephropathy in type 1 diabetes. *Am J Med* 1985; **78**: 785–794.
19. Kofoed-Enevoldsen A, Borch-Johnsen K, Kreiner Nerup J, Deckert T. Declining incidence of persistent proteinuria in Type 1 diabetes. *Diabetes* 1987; **36**: 785–794.
20. Rossing P, Rossing K, Jacobsen P, Parving H-H. Unchanged incidence of diabetic nephropathy in IDDM. *Diabetes* 1995; **44**: 739–743.
21. Reichard P, Rosenqvist U. Nephropathy is delayed by intensified insulin treatment in patients with insulin-dependent diabetes mellitus and retinopathy. *J Intern Med* 1989; **226**: 81–87.
22. Bojestig M, Arnqvist HJ, Karlberg BE, Ludvigsson J. Glyemic control and prognosis in type 1 diabetic patients with microalbuminuria. *Diabetes Care* 1996; **19**: 313–317.
23. Goldstein DE, Blinder KJ, Ide CH, Wilson RJ, Wiedmeyer HM, Little RR, *et al*. Glycaemic control and development of retinopathy in youth-onset insulin-dependent diabetes mellitus. *Ophthalmology* 1993; **100**: 1125–1131.

